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Static and Dynamic Stereochemistry of the Conformational Atropisomers of Tetra(*o*-tolyl)benzene

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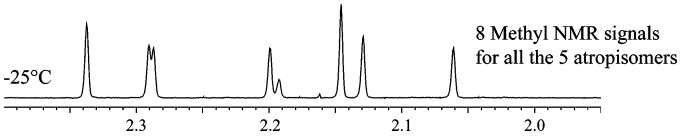


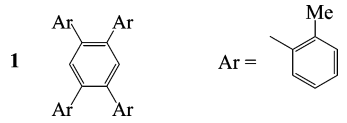
Whereas only one atropisomer of 1,2,4,5-tetra(*o*-tolyl)benzene was observed by X-ray diffraction in the solid, five conformational atropisomers were detected by low-temperature NMR in solution. Their structures were assigned by a combination of NOE experiments, solvent effect, and ab initio calculations. Variable temperature dynamic NMR and bidimensional EXSY experiments allowed the barrier for the interconversion of these atropisomers to be determined ($\Delta G^{\ddagger} = 15.3$ kcal mol^{-1}).

Introduction

Two equal aryl moieties, lacking a local 2-fold symmetry axis coincident with the bonds joining them to a central benzene ring, can originate, in principle, two conformers (stereolabile atropisomers) possibly with a different population. This is because the peripheral aryl substituents adopt a position not coplanar with the plane of the central ring. A few examples are reported [2−6] where two such atropisomeric conformations were detected by NMR spectroscopy: in some cases they even could be separated as configurationally stable compounds.[2,5]

When a greater number of aryl substituents are bonded to a benzene ring, two or more atropisomers can be populated, depending on the global molecular symmetry.[5,7−11] For instance, six equal *ortho*-substituted aryl groups bonded to a benzene ring comprise, in principle, eight atropisomers, seven of which were isolated as configurationally stable compounds.[9] On the other hand, four such aryl groups bonded to unsaturated moieties originate a number of conformational atropisomers that were detected by NMR spectroscopy.[10] Likewise, four aryl groups bonded to a benzene ring yield a number of conformational atropisomers,[11] although their structures were not assigned, nor the corresponding dynamic processes investigated. For this reason we report here a detailed study of the static and dynamic situation occurring in a compound having four *o*-tolyl substituents bonded to a benzene ring in the 1,2,4,5-positions, i.e., 1,2,4,5-tetra(*o*-tolyl)benzene **1**, as in Chart 1.

CHART 1



Results and Discussion

Owing to the degeneracy, the 16 forms available in principle to **1** are actually reduced to the five atropiso-

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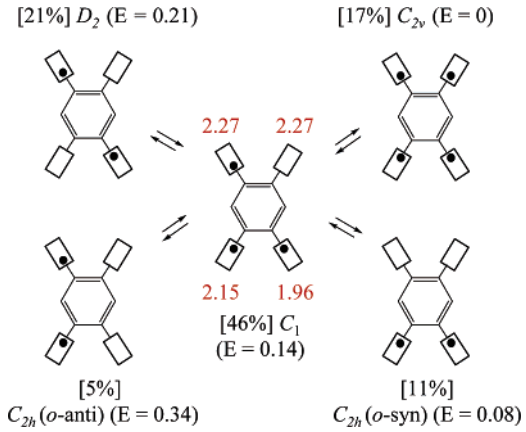
SCHEME 1. Five Possible Atropisomers of 1[a]



[a] Atropisomers are sketched with the orthogonal *o*-tolyl substituents represented by a box having a full dot to indicate when the methyl group is pointing toward the observer. The relative proportions (in square brackets) and the methyl shifts of C_1 (red, in ppm) refer to the spectrum of Figure 1 in CD_2Cl_2 at −65 °C. In parentheses are the relative computed energies in kcal mol^{-1}.

mers shown in Scheme 1. The atropisomer with symmetry C_1 is 8-fold degenerate since it comprises four equivalent pairs of enantiomers, the atropisomer D_2 is 2-fold degenerate since it comprises two enantiomers, and the other three atropisomers are also 2-fold degenerate since each comprises two identical forms (homomers). The two atropisomers belonging to the same C_{2h} point group are different because the two pairs of *o*-tolyl susbtituents in positions 1,2 and 4,5 can stay either in a syn or in an anti reciprocal relationship: they were thus labeled C_{2h} (*o*-syn) and C_{2h} (*o*-anti), respectively.

These five atropisomers correspond to the five energy minima resulting from ab initio calculations at the B3LYP/6-31G(d) level[12] (Supporting Information). These structures have quite similar energies, their differences not exceeding 0.34 kcal mol^{-1} (Scheme 1). These calculations also indicate that the *o*-tolyl substituents are not orthogonal to the plane of the central benzene ring, the corresponding dihedral angles covering the range 58−71°. In solution, however, the *o*-tolyl moieties are expected to librate about the orthogonal position with a very low barrier (the MM computed[13] values for these barriers are as low as 0.4 kcal mol^{-1}), thus yielding the "dynamic" symmetries of Scheme 1.

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(13) MMX force field as implemented in the computer package *PC Model*, v 7.5; Serena Software: Bloomington, IN.

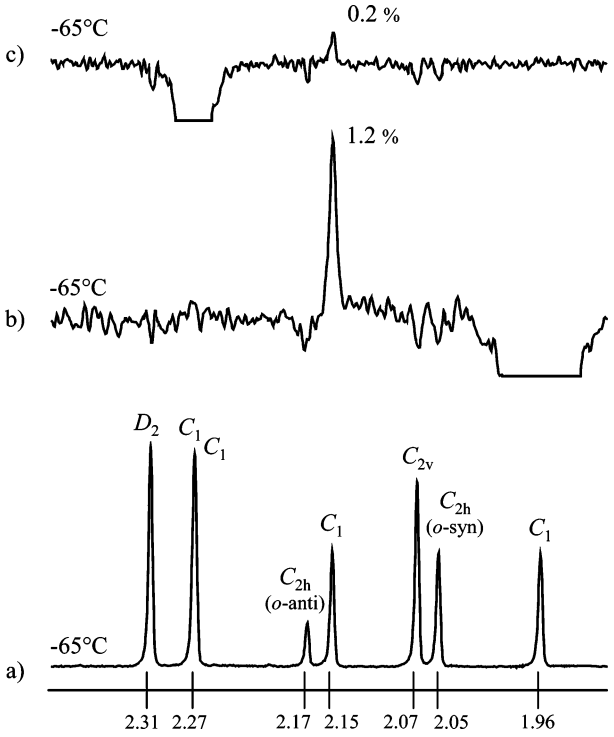

FIGURE 1. (a) ^{1}H NMR spectrum (600 MHz) of the methyl region of **1** in CD_2Cl_2 at −65 °C. (b, c) Two examples of NOE experiments at −65 °C (see text).

The room temperature ^{1}H NMR spectrum of **1** displays quite broad signals,[11] indicating that the atropisomers undergo an exchange process. Below −20 °C the lines become sharp, because the exchange rate has become slow with respect to the NMR time scale.

Atropisomer C_1, having four diastereotopic methyl groups, is expected to display four anischronous NMR methyl lines of equal intensity, whereas each of the other four atropisomers should exhibit a single methyl line since their methyl groups are either homotopic or enantiotopic: the relative intensities of these lines with respect to each other and with respect to the four lines of asymmetric C_1 depend on the population distribution. Eight methyl lines should be therefore detected if all five atropisomers are populated.

The ^{1}H NMR spectrum in CD_2Cl_2 at −65 °C (Figure 1) displays seven such lines, one of them (second from the left at 2.27 ppm) resulting from the accidental coincidence of two lines of equal intensity: this is confirmed by the observation that these lines could be resolved [11] in a different solvent (Figure 2, trace at −25 °C, where the relative shifts of the fourth and fifth lines from the right have been also interchanged).

The lines labeled C_1 in Figure 1 (trace a) have a precise 2:1:1 intensity ratio, which remains constant when other solvents or temperatures are employed, whereas measurable variations are observed for the relative intensities of the other signals. The three 2:1:1 lines must be thus assigned to the diastereotopic methyl groups of the asymmetric atropisomer C_1, which is found to be the most populated form (46%). This might be a consequence of its 8-fold degeneracy mentioned above and also of the favorable contribution to $\Delta G°$ of the entropic component $\Delta S°$. In fact C_1 is stabilized with respect to the other four

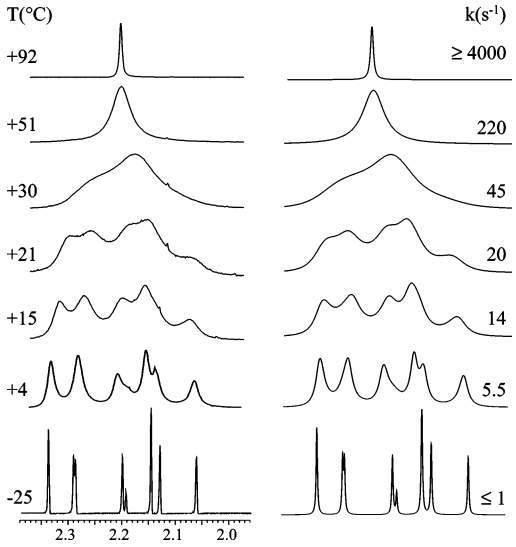

FIGURE 2. (Left) Temperature dependence of the eight ^{1}H NMR methyl signals of the five atropisomers of **1** in $CDCl_2$-$CDCl_2$ at 600 MHz. (Right) Line shape simulation obtained with the rate constants indicated (see text).

conformers by the entropy of symmetry, having the lowest symmetry number (i.e., $\sigma = 1$) and, being chiral, is further stabilized by the entropy of mixing (i.e., Rln2).[14] The shifts corresponding to the diastereotopic methyl groups of C_1 were assigned by means of NOE experiments that had to be carried out at −65 °C to make negligible the saturation transfer effect.

Excitation of the line at 1.96 ppm yields an enhancement (1.2%) on the line at 2.15 ppm, (Figure 1, trace b). In addition excitation of this line also enhances one of the two single lines of the central benzene ring (7.19 ppm) and the doublet of the hydrogen in position 3 of the same tolyl ring (7.01 ppm). Conversely, excitation of the line at 2.15 ppm also enhances one of the two single lines of the central benzene ring (7.15_5 ppm) and the doublet of the hydrogen in position 3 of the same tolyl ring (7.10 ppm). This indicates that the two lines at 1.96 and 2.15 ppm correspond to methyl groups in close proximity and must thus belong to the pair of tolyl substituents *ortho* to each other and in a syn relationship. As a consequence, the two accidentally coincident lines at 2.27 ppm correspond to the other pair of tolyl substituents, i.e., those that are *ortho* to each other but in an anti relationship. Excitation of these accidentally coincident lines at 2.27 ppm yields a very weak NOE effect (0.2%) on the line at 2.15 ppm (Figure 1, trace c): the latter line is therefore due to the tolyl group that is in a *meta* position and in a syn relationship with respect to one of the two tolyl substituents whose coincident methyl lines have been excited. It should also be pointed out that excitation of the two coincident lines at 2.27 ppm enhances six groups of signals in the aromatic region, i.e., the two single lines of the central benzene ring (7.15_5 and 7.19 ppm), the two accidentally coincident doublets of the hydrogens in position 3 of the tolyl rings being excited (both at 7.13 ppm) and the doublets of the hydrogen in position 6 of the same two tolyl rings (6.80 and 6.83 ppm). The latter result confirms that the rings exhibiting coincident methyl lines are *ortho* to each other and in the anti reciprocal relationship, since the methyl group of each of them is close to the H-6 of the other.

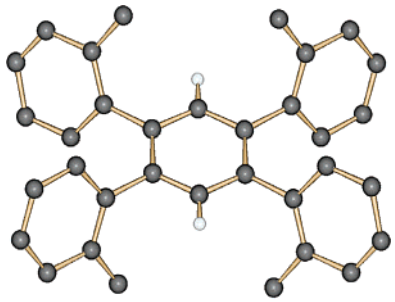

FIGURE 3. Single-crystal X-ray structure of compound **1**. The hydrogen atoms have been omitted, with the exception of those of the central benzene ring.

The average distance between the methyl hydrogens of the two syn tolyl substituents *ortho* to each other is computed to be 4.00 Å, whereas the corresponding distance for the syn tolyl substituents *meta* to each other is 5.28 Å. The ratio of these values, elevated to the sixth power (0.19), matches the reciprocal ratio of the corresponding NOE values (0.2/0.12 = 0.17). The methyl shifts of C_1 are indicated in red in Scheme 1.

X-ray diffraction shows that, in the solid, compound **1** adopts the structure shown in Figure 3, which has a C_i symmetry since the planes of the tolyl substituents in positions 1 and 4 are twisted with respect to the central benzene ring by 66.2° and those in positions 2 and 5 by 61.7° (Supporting Information). In the solid state, therefore, two methyl groups are different (diastereotopic) with respect to the other two. In solution, however, the mentioned libration process originates the dynamic C_{2h} (*o*-anti) symmetry of Scheme 1, which makes equivalent (enantiotopic) the four methyl groups, as experimentally observed (with the exception of asymmetric C_1, all of the other four atropisomers exhibit, in fact, a single NMR line for the four methyl groups).

Whereas the identification of atropisomer C_1 is straightforward, it is more difficult to assign the other four atropisomers. It is important, however, to try to relate, at least, the solid-state structure with one of the four symmetric atropisomers present in solution.

The lines due to the pair of atropisomers C_{2h} (*o*-anti) and D_2 can be unambiguosly distinguished from the pair C_{2h} (*o*-syn) and C_{2v} by means of NOE experiments. In the first case, in fact, by exciting either of the methyl lines, an enhancement of three sets of aromatic signals should be observed, i.e., the single line of the central benzene ring, the doublet due to the H-3 in the same tolyl being irradiated, and the doublet due to H-6 of the ring in an *ortho* position and in an antiparallel relationship to the tolyl being excited. Such a result was obtained by exciting the methyl lines at 2.17 and 2.31 ppm of Figure 1. In fact excitation of the line at 2.17 ppm enhances a single line at 7.16_5 ppm, a doublet at 7.09 ppm (H-3), and a doublet at 6.85 ppm (H-6). Likewise excitation at 2.31 ppm enhances a single line at 7.16 ppm, a doublet at 7.15 ppm (H-3) and a doublet at 6.78 ppm (H-6). The 2.17 and 2.31 ppm lines correspond therefore to C_{2h} (*o*-anti) and

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to D_2 atropisomers, although this experiment cannot identify which is which.

At −25 °C in $CDCl_2CDCl_2$ (Figure 2), as well as in CD_2Cl_2 at the same temperature (dielectric constants $\epsilon = 12$ and 11, respectively[15]), the integrated intensity ratio of these two lines is 3.8 ± 0.2, whereas in a more polar solvent, such as CD_3OD ($\epsilon = 40$ [15]), the ratio at the same temperature becomes 2.7 ± 0.1. This noticeable modification of the relative proportions might be interpreted as due to the fact that atropisomer D_2 is predicted, by ab initio calculations, to have a null dipole moment, contrary to C_{2h} (*o*-anti) for which a small, but not null, value is calculated (0.20 D). One would be thus tempted to suggest that the apolar form D_2 corresponds to the major of these two lines (2.31 ppm, Figure 1) and the slightly more polar C_{2h} (*o*-anti) to the minor one (2.17 ppm, Figure 1) because their relative intensities decrease and increase, respectively, with the solvent polarity. On this assumption the C_{2h} (*o*-anti) atropisomer should be the one corresponding to the crystal structure. This assignment parallels the trend of the two corresponding energies, in that D_2 is computed to be more stable than C_{2h} (*o*-anti) by 0.13 kcal mol^{-1} (Scheme 1). Calculations also indicate that C_{2h} (*o*-anti) is the least stable of the five atropisomers (Scheme 1), a feature compatible with the above assignment to the least intense line in the spectra of Figures 1 and 2. However these are circumstantial arguments that cannot rule out the possibility of a reverse assignment.

Excitation of the other two single methyl lines of Figure 1 (at 2.05 and 2.07 ppm) enhances only two sets of aromatic signal, i.e., the single line of the central benzene ring and the doublet of the H-3 in the same tolyl being irradiated. This unambiguously proves how these two lines correspond to the pair of atropisomers C_{2v} and C_{2h} (*o*-syn), since in their structures (see Scheme 1) the H-6 of the tolyl group *ortho* to that having its methyl irradiated is too far away to exhibit a NOE effect. [It was also observed that excitation of the line at 2.05 ppm also enhances a single line at 7.18 ppm and a doublet at 7.06 ppm (H-3) and excitation at 2.07 ppm enhances a single line at 7.17 ppm and a doublet at 7.07 ppm (H-3)]. Again this NOE experiment cannot determine which structure corresponds to which line.

Contrary to the previous case, the ratio of these two lines does not change appreciably in a polar solvent like CD_3OD, most likely because both atropisomers have a not null dipole moment, the computed values being, in fact, 0.61 and 0.42 D for C_{2v} and C_{2h} (*o*-syn), respectively. Owing to the lack of experimental evidence we reluctantly have to rely solely on computations for a tentative assignment. Ab initio calculations indicate C_{2v} to be more stable than C_{2h} (*o*-syn) by 0.08 kcal mol^{-1} (Scheme 1 and Supporting Information). On this basis one might identify the line at 2.07 ppm of Figure 1 as due to C_{2v} and that at 2.05 ppm as due to C_{2h} (*o*-syn), although a reverse assignment cannot be obviously excluded.

To clarify the mechanism of the exchange responsible for the temperature-dependent spectra of Figure 2, a 2D EXSY experiment was performed. In Figure 4 it is shown how each single line of the four symmetric atropisomers

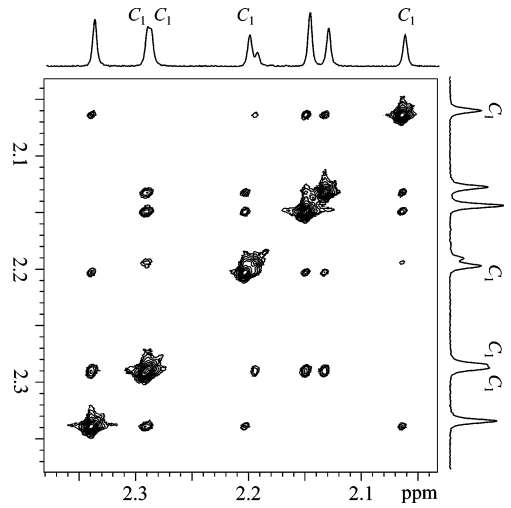

FIGURE 4. 2D EXSY experiment (600 MHz in $CDCl_2CDCl_2$) of the methyl region of **1** carried out at −25 °C with a mixing time of 100 ms (see text).

exchanges with all four anisochronous lines of C_1, whereas a direct exchange between the lines of the symmetric atropisomers does not occur. This result was taken into account in the simulations[16] of the spectra of Figure 2 (right), where the values of the rate constant (k, in s^{-1}) are reported at each temperature. The correctness of the simulations obtained with such a procedure proves that the interconversion involving the symmetric atropisomers occurs solely through the intermediacy of the asymmetric form C_1, as indicated in Scheme 1 (if a direct exchange between the lines of the symmetric atropisomers is assumed, an acceptable simulation cannot be obtained).

In principle four different k values should be used since there are four different transitions states connecting the symmetric conformers with the asymmetric C_1. However, these transition states have, conceivably, very similar energies, so that the related rate constants cannot be distinguished in a NMR experiment. Indeed ab initio calculations predict that the four computed barriers cover the very restricted range of 13.0−13.4 kcal mol^{-1} (Supporting Information). Thus a single k value was used at each temperature (Figure 2) and a unique free energy of activation ($\Delta G^{\ddagger} = 15.3 \pm 0.2$ kcal mol^{-1}) was derived for the whole process. As often observed in conformational NMR studies,[17] the $\Delta G^{\ddagger}$ value is nearly independent of temperature in the restricted temperature range examined, and thus the entropic term is almost null within the experimental errors (i.e., $\Delta S^{\ddagger} = -6 \pm 6$ eu, hence $\Delta H^{\ddagger} = 13.4 \pm 1.9$ kcal mol^{-1}). The difference between the computed and the experimental barrier is quite acceptable, given the complexity of the system.

(15) *Landolt-Bornstein*, Band II, Teil 6; Springer-Verlag: Berlin, Germany, 1959.

(16) PC version of the QCPE program *DNMR-6*, no. 633; Indiana University: Bloomington, IN.

(17) Hoogosian, S.; Bushweller, C. H.; Anderson, W. G.; Kigsley, G. *J. Phys. Chem.* **1976**, *80*, 643. Lunazzi, L.; Cerioni, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7484. Bernardi, F.; Lunazzi, L.; Zanirato, P.; Cerioni, G. *Tetrahedron* **1977**, *33*, 1337. Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979**, 3031; Cremonini, M. A.; Lunazzi, L.; Placucci, G.; Okazaki, R.; Yamamoto, G. *J. Am. Chem. Soc.* **1990**, *112*, 2915; Anderson, J. E.; Tocher, D. A.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731. Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4924.

It is also worth mentioning that calculations suggest that the rotation of each *o*-tolyl is essentially independent of that of the other three; in other words the motion of these groups is not a correlated process. When each of the *o*-tolyl substituents becomes almost coplanar with the central benzene ring in the transition state, the original positions of the other three substituents are not significantly modified.[18]

Experimental Section

1,2,4,5-Tetra(*o*-tolyl)benzene (1). Rather than the method proposed by Mitchell for the preparation of a similar compound,[19] compound **1** was obtained as reported in the more recent literature[11] and was purified by means of preparative HPLC (250 mm × 10 mm silica column, hexane/2-propanol 99/1), mp = 206 °C. Crystals suitable for X-ray diffraction were obtained by slow evaporation from hexane. The details of the X-ray structure are given in the Supporting Information.

NMR Measurements. ^{1}H NMR spectra were recorded at 600 MHz. The low-temperature NOE experiments were obtained by means of the DPFGSE-NOE sequence[20] using a "rsnob" selective pulse (typically 92.5 ms, to obtain a pulse 20 Hz wide) and a mixing time of 1.0 s. The low-temperature EXSY experiments were obtained by means of the standard NOESY sequence with a mixing time of 0.1 s. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Complete fitting of dynamic NMR line shapes was carried out (Supporting Information) using a PC version of the DNMR-6 program.[16]

Computations. Ab initio computations were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs[12] (the standard Berny algoritm in redundant internal and default criteria of convergence was employed). Harmonic vibrational frequency were calculated in order to ascertain the nature of all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies, whereas for each transition state the frequency analysis showed a single imaginary frequency. The corresponding optimized structures are reported in Supporting Information.

Acknowledgment. Thanks are due to Prof. W. B. Jennings, University College, Cork, Ireland and Prof. S. E. Biali, Hebrew University, Jerusalem, Israel for helpful comments. Financial support was received from the University of Bologna (funds for selected research topics and RFO) and from MIUR-COFIN 2003, Rome (national project "Stereoselection in Organic Synthesis").

Supporting Information Available: Computational details, crystal data including CIF file, and DNMR matrix exchange for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org

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(18) In particular, the twisting angles of the substituents in positions *meta* and *para* to the ring which rotates change by less than 5° and that in the *ortho* position by less than 20°. For a recent review on the mechanism of molecular rotors see: Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. *Chem. Rev*. **2005**, *105*, 1281−1376.

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